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Role of Blood Urea Nitrogen As A Marker in Early Prediction of Severity in Acute Pancreatitis : an Indian Perspective

KEYWORDS: BUN, SAP, BISAP score.

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ABSTRACT *BACKGROUND: Severe Acute Pancreatitis (SAP) is a significant medical and surgical problem needs early identification and management. Current predictive scoring systems for assessing severity are difficult to practice and have important limitations. The aim of the study is to assess Blood Urea Nitrogen (BUN) as a marker of severity and single prognostic indicator with best discriminating value to identify patients at risk of SAP.*

METHODS: 36 patients with Acute Pancreatitis (AP) were admitted and BUN levels were determined. Bedside Index for Severity in Acute Pancreatitis criteria (BISAP) and RANSON'S score was used to assess disease severity and mortality. Receiver operator characteristic curves plotted and cutoff value was determined for the variable of interest.

RESULTS: BUN at 24 hours has the best predictive value for SAP and for mortality with areas under the curve (AUC) of 0.992 (95% CI) and 0.961(95% CI) respectively with 24.17 as optimal cutoff.

CONCLUSIONS: BUN serves as a simple, quick and accurate predictor of severity and mortality in AP have comparable predictive power with BISAP and RANSON'S score.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of the pancreas, regional tissues around the pancreas, or remote organ systems.The prevalence of AP is estimated between 6 and 45 per 100,000 adults per year[1]. In 80% of the cases the disease is mild, with interstitial oedema, and leads to recovery within days or weeks.[3] Severe forms, characterized by local or systemic complications, are associated with severe morbidity and even death, in up to 15-20%.[3,4] Identification of patients at risk for complications and mortality early, within 24 hours, so called golden hours or therapeutic window in the course of AP is an important step in improving outcome.[2] Risk stratification of patients early in the course of disease is the most important aspect in the management of acute pancreatitis. Routine clinical and laboratory data and multifactorial clinical scores measured on admission and during the first 48 h of hospitalization are currently the standards of care used to predict whether or not intensive care support is needed to address inflammation-associated complications.[5] Current methods of risk stratification have important limitations. The Ranson[6] and modified Glasgow score[7] contain data not routinely collected at the time of hospitalization like LDH. In addition, both require 48 hours to complete, missing a potentially valuable early therapeutic window.[8] A new Scoring system, referred to as BISAP (Bedside Index for Severity in Acute Pancreatitis) was recently validated. [9]

It is also cumbersome to remember all the criteria and often some of the laboratory tests required to establish the score are not done routinely for these patients. An ideal prognostic system or marker should be available at admission, be simple, quick, cheap to measure and reproducible.[10] In severe acute pancreatitis, there is considerable extravasation of intravascular fluid into third spaces. Hemoconcentration has been shown to be an accurate predictor of necrosis and organ failure[11].The prognostic ability of measurements of Blood urea nitrogen (BUN) and hematocrit stems from the ability to mirror intravascular volume depletion, a critical risk factor for death in AP. In addition hematocrit and BUN also provide valuable feedback of patient's response to initial resuscitation. This study is intended to evaluate BUN as an indicator of severity and single prognostic indicator in acute pancreatitis and compare BUN with RANSON'S and BISAP criteria in prediction of SAP and mortality and to determine the best discriminating value of BUN for identifying patients at risk of SAP and mortality.

MATERIAL AND METHODS

This is a prospective observational study. It includes all patients with symptoms of <24 hours presenting to the Emergency and OutPatient Department of Osmania General Hospital from April 2011 to October 2012 with acute pancreatitis. Patients with changes of chronic pancreatitis and Patients presenting ≥24 hours after symptom onset are excluded.

The diagnosis of AP was based on the presence of two of the following three features: (i) abdominal pain characteristic of AP, (ii) serum amylase and / or lipase ≥ 3 times the upper limit of normal, and (iii) characteristic findings of AP on abdominal imaging (USG/CECT scan). The Revised Atlanta Classification is used to assess disease severity, it categorizes severity in to three levels 1) Mild (lacks both

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organ failure, local or systemic complications 2) Moderately Severe (Organ failure is <48 hours duration, local complications, and /or exacerbation of coexistent disease 3) Severe Acute Pancreatitis (persistence of organ failure for >48 hours)[12]. Organ failure is defined by presence of shock (systolic blood pressure < 90 mm Hg), pulmonary insufficiency (arterial PO_2<60 mm Hg at room air or the need for mechanical ventilation), or renal failure (<100ml urine/24 h or serum creatinine level >2 mg/dl after rehydration).Systemic inflammatory response syndrome (SIRS) is defined by the presence of 2 or more of the following criteria: pulse >90 beats/min, respirations >20 per min, or $PaCO_2$ < 32 mm Hg, temperature >100.4°F or <96.8°F and white blood cell count >12,000 or <4,000 cells per mm^3or >10% immature neutrophils (bands).

Data collected on standard proformas detailing the medical history, physical examination and investigations. The investigations that sent at the time of admission ('0'hours) in all cases are serum amylase, WBC , RBS, LDH, SGOT, BUN, ABG, CXR and the investigations that sent at 48 $\pm$ 6 hours are Haematocrit ,BUN, S.Calcium, S.Bicarbonate, ABG, RBS, S.Albumin, LDH, CECT Abdomen. BISAP scores were calculated using above data from the first 24 h from admission and the RANSON'S score using data from the first 48 h. In addition BUN values were also obtained at 24 $\pm$ 6 hours. The BISAP score provides a single point for 5 parameters: BUN >25 mg/dL, impaired mental status, SIRS, age >60years, and/or the presence of a pleural effusion, for a possible total of 5 points. There was steady increase in mortality with increasing points.[9]

All patients were followed up throughout the hospital stay and the outcome of disease noted.

Statistical Analysis: Continuous variables such as BUN were presented as mean ± SD. Sensitivity, specificity, Positive and negative predictive values (PPV, NPV) were calculated for individual criteria. ROC curves were plotted and a cutoff value was determined for the variable of interest.

The individual prognostic criteria's were compared with the outcome and statistically analyzed to validate the significance of scores. Univariate analysis for continuous variables was conducted with the unpaired Student's t test. Categorical variables were analysed by the chi square test or Fisher's exact test. Significance level was set at $p < 0.05$.

RESULTS AND ANALYSIS

36 patients with Acute Pancreatitis were included in the study, of these 33 were male and 3 were female. Mean age of the study subjects was 38.47 $\pm$ 11.01. **(Table1)** shows demographic data of patients, 75% of the Pancreatitis was due to alcohol 86.12% (27/36), followed by gallstones in 13.88% (5/36). 9 out of 36 patients (25%) had persistent OF and classified as SAP, while 27 had non severe course. Renal failure was present in 7 out of 9 patients (77.77%), respiratory failure in 6 (66.66%) and cardiovascular failure/shock in (88.88%) patients with SAP. 5 out of 9 patients with SAP died during the course of illness while all patients with non severe course survived.**(Table 2)** Mean BUN (at admission, at 24 hours and 48 hours) , BISAP, and RANSON scores were significantly higher among SAP group (p<0.0001) Vs Non severe pancreatitis group.

(Table 3) shows BUN ≥25 mg/dl at 24 or 48 hours has sensitivity of 89, specificity of 100, PPV of 100 and NPV of 96, and overall diagnostic accuracy of 97.22% in predicting development of SAP. While bringing down the BUN cut off to ≥20 mg/dl at 24 hours increased sensitivity and NPV to 100% and decreased specificity and diagnostic accuracy to 75% and 91.6 % respectively**.** BISAP Score ≥3 has specificity similar to BUN Rise ≥5 mg/dl at 48 hours (96.29%) but sensitivity is low (77.77%). ROC curves were plotted for BUN (at admission, at 24 hours), BISAP, and RANSON scores to know prediction of SAP **(fig 1,2,3).** AUC and optimal cut off were determined as shown in (**Table 4)**.

(Table 5,6) determines that all criteria have 100% NPV for predicting patients at risk of dying while specificity is better for BISAP (90%) and BUN ≥25 mg/dl at admission and at 24 or 48 hours (90 and 94%) and worse for RANSON score (42%). For mortality prediction ROC curves plotted **(fig 4,5,6).**

DISCUSSION

Acute pancreatitis (AP) is a major burden in ICU and accurate risk stratification is essential for better utilization of resources. Current prognostic markers in AP have important limitations. Majority require lab parameters that are not routinely measured and most studies that examining routine laboratory markers have focused on necrosis and organ failure rather than mortality.

Persistent organ failure is a major contributing factor to morbidity and mortality of AP. Early identification of patients at risk for organ failure helps in triage and aggressive preventive measures, such as vigorous fluid resuscitation. Successful correction of organ failure within 48 hours leads to a drop in mortality to almost 0%.[13] The multifactorial scoring systems like RANSON[6], GLASGOW[7], APACHE II[14] have several disadvantages that prevent their routine use in daily practice. The RANSON score is only valid for the first 48 hours and APACHE II score uses parameters that are used only in the ICU setting and their determination is time-consuming and expensive. In addition to the established clinical scores, a variety of single markers like C-reactive protein have emerged for acute pancreatitis[15].

Arnell et al reported that BUN is an independent predictor for the need of ICU treatment in biliary pancreatitis[16]. BUN ≥ 12mmol (33 mg/dl) was found to be an independent predictor of development of adverse events[16]. Wu et al studied incremental BUN in relation to SAP and mortality. However, the role of isolated elevated BUN on admission or in the course of the disease has only scarcely been studied.[16,17] BUN was chosen because of its high predictive value because it is an integral marker of tissue necrosis, protein catabolism, and renal function and it serves as a surrogate of intravascular volume status and is also a physiological variable that changes in response to therapy. In addition it is simple and routinely used.

In our study Alcohol was the most common cause of AP followed by gall stones in contrast to previous studies where gall stones were the most common cause of AP.[18]

Faisst etal observed that mortality in patients with elevated BUN on admission was significantly increased (nonsurvivors: 39 ± 30 vs survivors: 17 ± 11 mg/dL; P=0.028; PPV 67%, NPV 82%).[19] We noted similar trend, with significantly higher BUN at admission among non survivors (nonsurvivors: 43.97 ± 29.7 vs survivors: 14.83±12.1 mg/d; P=0.0004). We noted BUN ≥20 mg/dl at admission has PPV of 80% and NPV of 96% for predicting SAP with 89% sensitivity and 93% specificity. BUN ≥25 mg/dl at 24 hours is highly specific with PPV of 100% for prediction

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of SAP, and NPV of 89% and may miss few cases which may require ICU care and aggressive management protocol. This can be overcome by reducing BUN threshold to ≥20 mg/dl, which identifies all the cases of SAP at the cost of specificity. BUN Rise ≥5 mg/dl at 48 hours has PPV of 88.87% and NPV of 96.29% for predicting SAP. The utility of isolated elevated BUN on admission or in the course of the disease for categorizing subjects into high (SAP) and low-risk groups was proved, and BUN was proved to be a factor that is closely associated with the development of organ failure or SAP. BISAP score correlated well with SAP. From our analysis AUC of BUN at 24hours for prediction of SAP and mortality was 0.992 and 0.961 with optimal cutoff value of >24.17 and for BISAP, RANSON score was 0.934 and 0.975 respectively for prediction of SAP.

In addition AUC for BISAP was better 0.955 for predicting mortality with an optimal cut off >2. Interestingly RANSON'S has the best discriminative value for prediction of mortality with AUC of 1.0 (0.903-1.0) with optimal cut off of >7.Thus BUN, BISAP and RANSON'S in this study were found to be accurate for risk stratification and predicting mortality. In fact BUN performed better than more complex scoring systems such as RANSON'S for identifying those at risk of organ failure and SAP. Increasing BUN and BISAP score correlated with increased SAP and mortality ($p<0.001$).

CONCLUSIONS

BUN serves as a simple and accurate predictor of severity and mortality in AP. BUN ≥20 mg/dl at 24 hours is highly sensitive for prediction of SAP and can be used as criteria for ICU transfer (NPV of 100%). BUN ≥25 mg/dl at 24 hours is highly specific for prediction of SAP and aggressive treatment is warranted (PPV of 100%). BUN at 24 hours has the best predictive value for mortality with AUC of 0.996 with 24.17 as optimal cut off. BUN ≥25 mg/dl at any time up to 48 hours has high NPV of 100% for mortality. BISAP score within the first 24 h of admission stratifies patients according to their risk of mortality and onset of organ failure.

Table 1: PATIENT DEMOGRAPHICS AND OUTCOMES

	Total (36)	Severe pancreatitis (9)	Non severe pancreatitis(27)	p value
Age in years (mean ± SD)	38.47 ± 11.01	41.89 ± 12.68	37.33 ± 10.41	0.55 (NS)
Sex (M:F)	33:3	9:0	27:3	0.55 (NS)
Etiology				
Alcohol	27	8	19	-
Gall stones	5	1	4	-
Post ERCP	1	0	1	-
Trauma	1	0	1	-
Malignancy	1	0	1	-
Idiopathic	1	0	1	-
Hospital stay in days	10.54 ± 6.59	12.44 ± 7.92	9.89 ± 5.71	0.2996(NS)
ICU stay in days	2.36 ± 2.79	5.67 ± 3.91	1.26 ±0.86	<0.0001
Mortality (%)	5 (13.89)	5 (55.55)	0 (0)	<0.0001
Necrotising pancreatitis	14/29(48.27%)	5/5(100%)	9/24(37.5%)	0.0169

Table 2: Clinical, Laboratory and Imaging Characteristics Of Cases

Units as Mean ± SD	Total (36)	Severe pancreatitis (9)	Non severe pancreatitis(27)	p value
BISAP SCORE	1.44 ± 1.18	3 ± 1	0.93 ± 0.68	<0.0001
BUN at admission mg/dl	18.88 ± 18.19	39.88 ± 26.54	11.88 ± 5.02	<0.0001
BUN at 24 hours	21.61 ± 19.80	46.05 ± 27.26	13.28 ± 4.86	<0.0001
BUN at 48 hours	21.13 ± 20.27	47.70 ± 25.78	11.91 ± 4.93	<0.0001
Ranson score	3.56± 2.58	7.11 ± 2.37	2.37 ± 1.18	<0.0001

Table 3: Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value And Diagnostic Accuracy Of Different Criteria For Prediction Of Severe Acute Pancreatitis.

Criteria used (critical value)	Sensitivity (percentage)	Specificity (percentage)	Positive predictive value (percentage)	Negative predictive value (percentage)	Accuracy of diagnostic test (percentage)
BISAP SCORE ≥3	77.77	96.29	87.48	92.86	91.66
BUN≥20 mg/dl at admission	89	93	80	96	91.66
BUN ≥25 mg/dl at 24&48 hours	89	100	100	96	97.22
BUN ≥20 mg/dl at 24 hours	100	75	89	100	91.66
BUN Rise ≥5 mg/dl at 48 hours	88.88	96.29	88.87	96.29	94.44
RANSON SCORE ≥3	100	74.07	56.25	100	80.55

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Table 4 : AUC Of Different Scoring Systems In Predicting SAP

Criteria	AUC (95% CI)	Optimal cut off
BUN at 24 hours	0.992 (0.887- 1.0)	>24.17
BUN at admission	0.949 (0.819- 0.994)	>21.47
BUN at 48 hours	0.996 (0.895- 1.0)	>24.27
BISAP	0.934 (0.799-0.99)	>2
RANSON SCORE	0.975 (0.86-1.0)	>4

Table 5 : Sensitivity, Specificity, PPV, and NPV Of Different Scoring Systems In Predicting Mortality

Criteria used (critical value)	Sensitivity (percentage)	Specificity (percentage)	Positive predictive value (percentage)	Negative predictive value (percentage)	Accuracy of diagnostic test (percentage)	
BISAP SCORE ≥3		100	90	63	100	91.66
BUN ≥25 mg/dl at 24 hours	100	90	63	100	91.66	
BUN≥20 at admission	100	94	71	100	94.44	
BUN ≥25 mg/dl at 48 hours	100	94	71	100	94.44	
BUN rise ≥5mg/ dl at 48 hours	100	94	71	100	94.44	
RANSON SCORE≥3	100	42	22	100	50	

Table 6: AUC Of Different Scoring Systems In Predicting Mortality

Criteria	AUC (95% CI)	Optimal cut off
BUN at 24 hours	0.961 (0.838-0.998)	24.17
BUN at admission	0.961(0.838-0.998)	>28
BUN at 48 hours	0.974 (0.858-0.99)	>33.59
BISAP	0.955 (0.28-0.996)	>2
Ranson score	1.0 (0.903-1.0)	>7

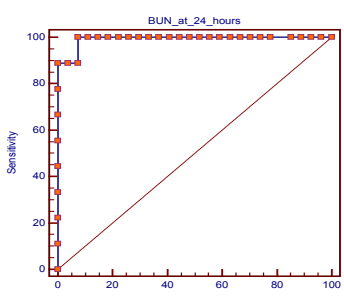

Figure 1: ROC curve of BUN at 24 hours for prediction of SAP

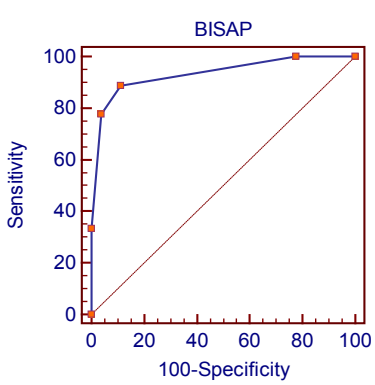

Figure 2: ROC curve of BISAP for prediction of SAP

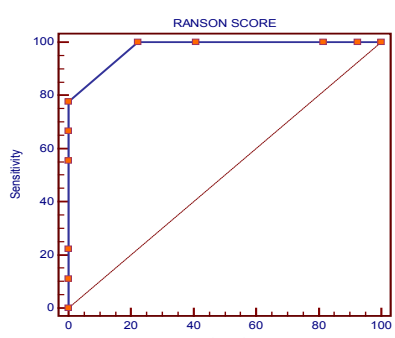

Figure 3: ROC curve of RANSON score for prediction of SAP

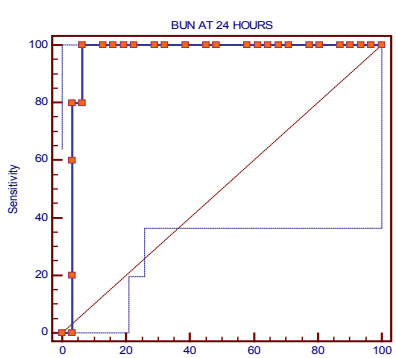

Figure 4: ROC curve of BUN at 24 hours for prediction of mortality

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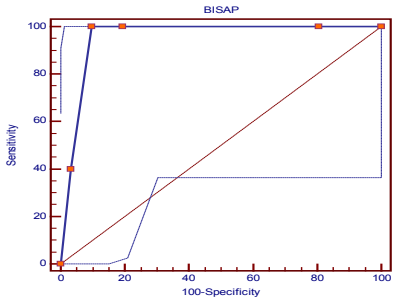

Figure 5: ROC curve of BISAP for prediction of mortality

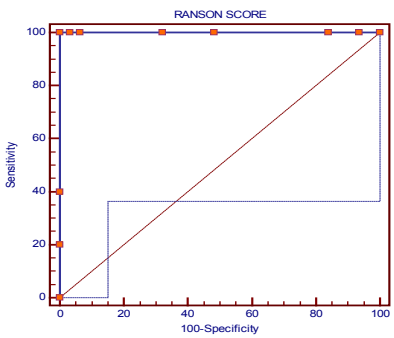

Figure 6: ROC curve of RANSON score for prediction of mortality

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